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# Nasal nitric oxide is a marker of poor asthma control

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## Abstract

Asthma control, evaluated by symptoms, exacerbations rate and lung function may be greatly influenced by comorbidities, particularly chronic rhinosinusitis (CRS). Measurement of nasal nitric oxide (nNO) is a simple way to assess the severity of CRS. We aimed to analyze the relationship between asthma control and nasal NO. All patients with moderate-to-severe asthma on regular follow-up at our Outpatients' Clinic between November 2009 and April 2010 were included into the study. All patients were evaluated for asthma control by asthma control questionnaire (ACQ) and comorbidities (rhinitis, chronic rhinosinusitis with (CRSwNP) or without nasal polyps, obesity). Exhaled nitric oxide and nNO were obtained in all patients. Eighty-two patients were enrolled (mean age: 48 years, range: 21–80; 42 females). According to ACQ, 53 patients (64.6%) reported controlled asthma. Patients with uncontrolled asthma had lower nNO and higher prevalence of CRSwNP, with a significant correlation between nNO and ACQ. nNO is a biomarker negatively related to asthma control. As low nNO values were associated to CRSwNP, our results indicate that asthma control is highly influenced by this comorbidity.

## List of abbreviations

|                    |  |
|--------------------|--|
| ACQ                | asthma control questionnaire           |
| ACT                | asthma control test                    |
| BMI                | body mass index                        |
| Calv <sub>NO</sub> | alveolar concentration of nitric oxide |

|                   |   |
|-------------------|---|
| CRS               | chronic rhinosinusitis                      |
| CRSsNP            | chronic rhinosinusitis without nasal polyps |
| CRSwNP            | chronic rhinosinusitis with nasal polyps    |
| CT                | computed tomography                         |
| FE <sub>NO</sub>  | fraction of exhaled nitric oxide            |
| Jaw <sub>NO</sub> | bronchial flux of nitric oxide              |
| nNO               | nasal nitric oxide                          |
| NSAID             | non-steroidal anti-inflammatory drugs       |

## Introduction

Asthma is a chronic inflammatory airway disease characterized by airway hyper-responsiveness and reversible bronchial obstruction [1]. Based on this definition, current asthma therapy is based on a variable combination of anti-inflammatory (mainly inhaled corticosteroids) and bronchodilating drugs. Asthma guidelines recommend to modulate the therapy according to asthma control, defined as patient's current and recent level of symptoms and functional status. Many data support the recommendation that having a high level of current control improves stability and reduces the risk of exacerbations [2]. Easy-to-administer questionnaires have been developed in recent years to help clinicians to monitor asthma control of their patients. Among the most used questionnaires are asthma control test (ACT) [3] and asthma control questionnaire (ACQ) [4]. Both questionnaires explore patients' symptoms, referred to the last four weeks in case of ACT and for the last week in case of ACQ, for which FEV<sub>1</sub> measurement is also required. Nevertheless, even among patients treated according to guidelines, control of asthma is still not reached by a great proportion of patients, ranging from 20% to 70% [5].

Different asthma comorbidities may impact on asthma control, worsening symptoms and/or contributing to airway inflammation. Among the most frequently encountered comorbid conditions associated to asthma are rhinosinusitis, gastro-esophageal reflux disease and obesity.

With respect to chronic rhinosinusitis, it has been reported that 90% of patients with mild to moderate asthma and almost 100% of those with severe asthma, have radiological abnormalities of the sinuses [6]. Chronic rhinosinusitis has been associated with both more severe and more difficult to control asthma [7] and ten Brinke *et al* [8] found extensive sinus disease associated with eosinophilic airway inflammation in 24% of patients with severe asthma.

Low values of nasal NO (nNO) have been reported in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) [9, 10], and damage of the ciliated epithelium of the paranasal sinuses and the size of the paranasal sinus ostia have been suggested as explanatory mechanisms. An inverse relationship between nNO concentration and the extent of sinus disease, as documented by CT, was observed [11]. For these reasons, we wished to measure nNO as a marker of sinus involvement in asthmatic patients and to test its relationship with asthma control.

To this aim we investigated the determinants of uncontrolled asthma by evaluating the relative role of the most common asthma co-morbidities (rhinitis, chronic rhinosinusitis with (CRSwNP) and without

nasal polyps (CRSsNP), obesity) and non-invasive markers of sinus involvement (nNO) and airway inflammation (exhaled nitric oxide ( $FE_{NO}$ ) and its alveolar concentration ( $Calv_{NO}$ ) and bronchial flux ( $Jaw_{NO}$ )).

## Methods

### Patients

Eighty-two non-smoking consecutive patients (42 women) aged 21–80 years (mean age 48 years) with previously diagnosed moderate-to-severe asthma according to GINA international guidelines [1] and in regular follow-up at Outpatient Asthma Clinic of AO Mauriziano ‘Umberto I’ Hospital of Turin between November 2009 and April 2010 (six months) were included into the study.

All the patients were queried regarding symptoms of rhinitis and underwent skin prick to a panel of 14 common inhalant allergens. Atopy was defined as the presence of at least one positive skin prick test (wheal diameter  $>3$  mm compared to negative control) to inhalant allergens. All the patients complaining of nasal blockage/obstruction and discolored discharge or reduction in sense of smell or facial pain/pressure for  $>3$  months were referred to an ear, nose and throat specialist for nasal endoscopy and/or CT scan of the sinuses. CRS was confirmed by the presence of two of the above-mentioned symptoms and endoscopic signs (polyps, mucopurulent discharge from middle meatus, edema/mucosal obstruction primarily in middle meatus) and/or CT signs of mucosal changes within ostiomeatal complex and/or sinuses [12]. Using previously published Lund–Mackay cutoff scores of 2 or more, cases were classified based on the radiographic extent of disease in patients with and without CRS [13].

Body mass index (BMI) was calculated in every patient. None of the enrolled patients were using intranasal corticosteroids.

Forty non-smoking subjects, matched for age, served as control for nitric oxide measurements. All patients and controls gave their written consent to participate to the study, which was approved by local Ethics Committee (Comitato Etico Interaziendale N: 146/2009).

### Exhaled nitric oxide

Exhaled NO was measured at 50, 100 and 200 ml  $s^{-1}$  with a chemiluminescence analyzer (NIOX, Aerocrine AB, Solna, Sweden), according to current recommendations [14].

NO output was plotted against exhalation flow rate at flow rates 50–200 ml  $s^{-1}$ , and a regression line was set between these variables. All subjects had a correlation coefficient  $>0.95$  in the regression analysis. Alveolar NO concentration ( $Calv_{NO}$ ) and bronchial NO flux ( $Jaw_{NO}$ ) are the slope and intercept of the regression line, respectively [15].

Axial backward diffusion of NO from bronchial compartment to alveoli may cause falsely high  $Calv_{NO}$  and falsely low  $Jaw_{NO}$  especially in subjects with increased  $Jaw_{NO}$ .  $Calv_{NO}$  and  $Jaw_{NO}$  adjusted for trumpet-shaped airways and axial diffusion ( $Calv_{NO}$  [TMAD] and  $Jaw_{NO}$  [TMAD]) were calculated according to the equations described by Condorelli *et al* [16].

### Nasal nitric oxide

Measurements were obtained using the same chemiluminescence NO analyzer (NIOX; Aerocrine AB, Solna, Sweden) calibrated with a certified NO calibration gas mixture according to European Respiratory Society/American Thoracic Society recommendations [14]. The patients were relaxed and in a sitting position. They were asked to insert a NIOX nasal olive into one nostril. They then inhaled to total lung capacity for more than 2 to 3 s through open mouths, after which they closed their mouths and held their breath while NO was continuously measured at an aspiration flow rate of 5 ml  $s^{-1}$ .

**Table 1.** Demographical, functional and inflammatory parameters in patients with asthma and healthy subjects.

|   | Patients ( <i>n</i> = 82) | Healthy subjects ( <i>n</i> = 40) | <i>p</i> -value  |
|---|---------------------------|-----------------------------------|------------------|
| Age (median age, range)                     | 48.0, 21–80               | 49.4, 18–78                       | 0.986            |
| Gender (M/F)                                | 40/42                     | 10/10                             | 0.998            |
| Atopy ( <i>n</i> , %)                       | 62 (75.6%)                | 4 (20.0%)                         | <b>&lt;0.001</b> |
| BMI (mean $\pm$ DS)                         | 24.1 $\pm$ 2.9            | 25.6 $\pm$ 2.8                    | 0.975            |
| FEV <sub>1</sub> % pr. (mean% $\pm$ DS)     | 89.0 $\pm$ 16.6%          | 97.2 $\pm$ 13.2%                  | <b>0.002</b>     |
| FEV <sub>1</sub> /VC (mean% $\pm$ DS)       | 70.3 $\pm$ 8.9%           | 82.3 $\pm$ 7.5%                   | <b>0.001</b>     |
| FEF <sub>25–75</sub> % pr. (mean% $\pm$ DS) | 56.2 $\pm$ 27.5%          | 72.6 $\pm$ 22.9%                  | <b>0.001</b>     |
| FE <sub>NO</sub> (mean ppb, IC95%)          | 43.9 (33.0–54.7)          | 16.2 (14.6–17.9)                  | <b>0.001</b>     |
| nNO (mean ppb $\pm$ DS)                     | 628.8 $\pm$ 411.9         | 1023.4 $\pm$ 342.8                | <b>0.002</b>     |
| Jaw <sub>NO</sub> (mean nl/s, IC95%)        | 2.29 (1.64–2.94)          | 0.61 (0.32–0.83)                  | <b>&lt;0.001</b> |
| Calv <sub>NO</sub> (mean ppb, IC95%)        | 5.13 (3.15–7.12)          | 1.6 (1.1–2.2)                     | <b>&lt;0.001</b> |
| Inhaled Budesonide equivalent (mcg, IC95%)  | 711.2 (542.1–880.3)       | N/A                               |                  |

We took into consideration the NO levels that were recorded at the plateau, which occurs after 20 to 30 s in most patients. The nasal olive was then placed in the other nostril and the test was repeated. Measurements were made in triplicate on both nostrils, and the highest mean value, from which the ambient NO level was subtracted, was considered.

### Assessment of asthma control by ACQ

#### ACQ

It consists of seven items: six questions, five related to symptoms during the last week and one related to the use of short-acting beta2 agonists, and the seventh item is an objective measure—a spirometric assessment (FEV<sub>1</sub>% predicted). Each item has seven alternatives of answer, scored from 0 to 6. The ACQ score is the mean of all these individual answers and therefore, it ranges also from 0 to 6 with higher scores standing for poorer control of asthma. A score of  $\leq 0.75$  has been associated with ‘well-controlled’ asthma while a score  $\geq 1.5$  has been associated with ‘not well-controlled’ asthma [4].

#### Lung function

Measurements of lung function were done with a water- sealed spirometer (Biomedin, Padua, Italy). The best of three measurements was automatically chosen by software. The parameters of interest were FEV<sub>1</sub>, FEV<sub>1</sub>/FVC ratio%, FEF<sub>25–75</sub>%.

#### Statistics

Statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA).

The Kolmogorov–Smirnov test was used to evaluate the normality of distribution of each continuous variable, and depending on the result of this test, the Student *t*-test or Mann–Whitney test were used to compare variables. Categorical variables were compared with the Fisher exact test.

Values are presented as mean (95% confidence interval). Stepwise multiple regression analysis has been performed to evaluate the effect of demographical, physical and inflammatory variables (age, gender, atopy, BMI, budesonide equivalent of inhaled corticosteroid therapy, FE<sub>NO</sub> and nNO) on ACT and ACQ values as dependent variables. Correlations between any significant determinant of asthma control and known comorbidities have been evaluated.

A *p*-value of  $<0.05$  was considered statistically significant.

## Results

Eighty-two patients with a diagnosis of moderate-to-severe asthma were enrolled (mean age 48 years, range 21–80; 42 females; mean BMI 24.1  $\pm$  2.9; 1 smoker; 4 with NSAID intolerance).

Demographic data, lung function and nitric oxide parameters obtained in patients and controls are summarized in table 1. Atopy prevalence was higher in patients with asthma than in healthy controls (75.6% versus 20% *p* < 0.001). Spirometric parameters were significantly reduced in patients compared to controls (table 1). Mean values of FE<sub>NO</sub>, Jaw<sub>NO</sub> and Calv<sub>NO</sub> were significantly higher while nNO oxide values were significantly lower in patients than controls (table 1). According to ACQ (ACQ  $\leq 1.5$ ), 54 patients (65.8%)

reported controlled asthma (table 2). Mean nNO was significantly lower in patients with non-controlled asthma,  $ACQ > 1.5$  ( $481.6 \pm 390.6$  ppb versus  $705.1 \pm 405.2$  ppb,  $p = 0.018$ ), who showed a higher prevalence of CRSwNP compared to patients with  $ACQ \leq 1.5$  (16/28, 57.1% versus 18/54, 33.3%,  $p = 0.038$ ).

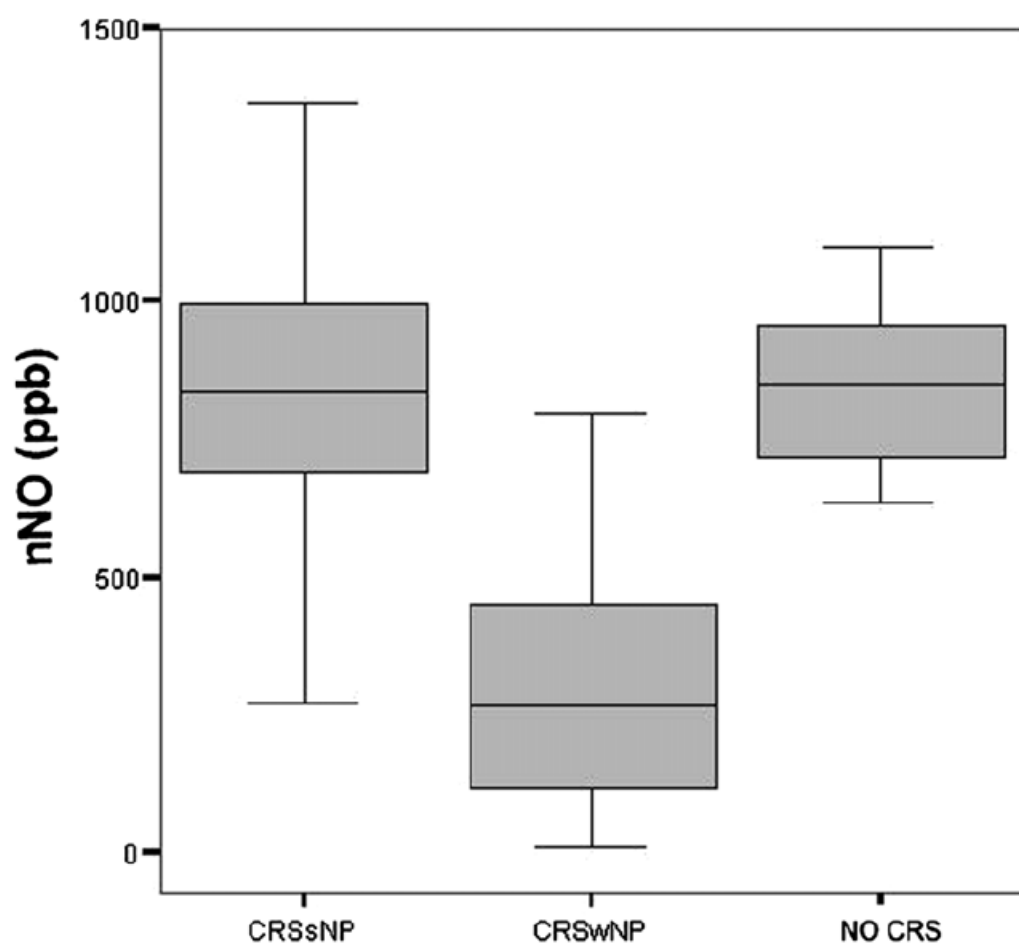
Patients with CRSwNP had significantly higher ACQ values ( $1.36 \pm 1.04$ ) compared to patients with CRSsNP ( $0.66 \pm 0.62$ ,  $p = 0.033$ ) and patients without CRS ( $0.53 \pm 0.62$ ,  $p < 0.001$ ).

No significant correlation between mean responses to any of the seven items of ACQ and nNO levels and/or presence of nasal polyps was found.

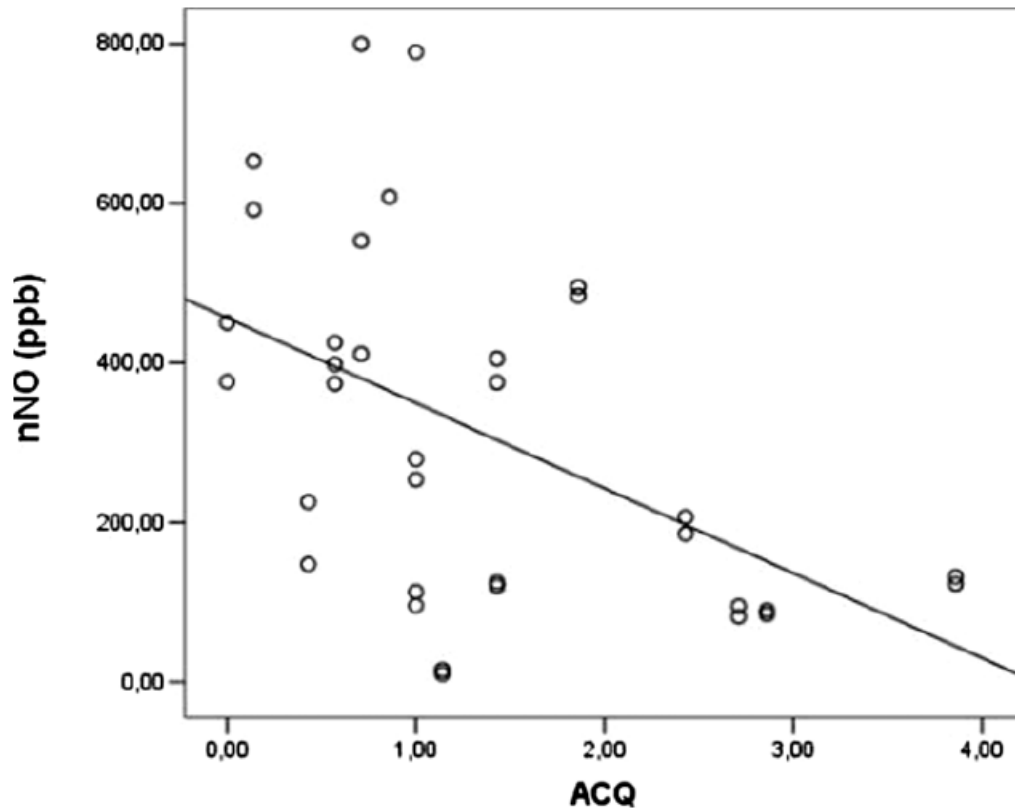
Median Lund–Mackay CT score was significantly higher in patients with CRSwNP (13, 95%IC: 8–20) compared to patients with CRSsNP (3, 95%IC: 2–5,  $p < 0.001$ ) and to those without CRS (1, 95%IC: 0–1,  $p < 0.001$ ).

**Table 2.** Demographic, functional and inflammatory parameters in patients with controlled versus uncontrolled asthma according to ACQ.

|   | Patients with<br>controlled asthma<br>( $ACQ \leq 1.5$ ) ( $n = 54$ ) | Patients with<br>uncontrolled asthma<br>( $ACQ > 1.5$ ) ( $n = 28$ ) | <i>p</i> -value |
|---|---|--|-----------------|
| Age (median age, range)                     | 47.5, 21–80   | 50.1, 32–59  | 0.707           |
| Gender (M/F)                                | 32/22   | 8/20   | 0.138           |
| Atopy ( $n, \%$ )                           | 43 (79.6%)  | 19 (67.8%)   | 0.342           |
| BMI (mean $\pm$ DS)                         | $24.1 \pm 2.7$  | $24.0 \pm 3.7$   | 0.758           |
| Patients with CRS ( $n, \%$ )               | 23 (42.6%)  | 18 (64.3%)   | 0.097           |
| Patients with CRSwNP ( $n, \%$ )            | 18 (33.3%)  | 16 (57.1%)   | <b>0.038</b>    |
| FEV <sub>1</sub> % pr. (mean% $\pm$ DS)     | $91.5 \pm 15.5$   | $79.1 \pm 19.2$  | 0.06            |
| FEV <sub>1</sub> /VC (mean% $\pm$ DS)       | $70.6 \pm 9.4$  | $69.5 \pm 7.8$   | 0.763           |
| FEF <sub>25–75</sub> % pr. (mean% $\pm$ DS) | $59.8 \pm 26.5$   | $44.9 \pm 30.4$  | 0.198           |
| FE <sub>NO</sub> (mean ppb, IC95%)          | 40.6 (28.8–52.4)  | 57.0 (26.1–87.9)   | 0.107           |
| nNO (mean ppb $\pm$ DS)                     | $705.1 \pm 405.2$   | $481.6 \pm 390.6$  | <b>0.018</b>    |
| Jaw <sub>NO</sub> (mean nl/s, IC95%)        | 2.03 (1.46–2.59)  | 3.34 (0.63–6.05)   | 0.104           |
| Calv <sub>NO</sub> (mean ppb, IC95%)        | 5.24 (2.82–7.65)  | 4.72 (1.43–8.01)   | 0.836           |
| Inhaled Budesonide equivalent (mcg, IC95%)  | 658.7 (461.5–856.0)   | 950.0 (550.0–1350.0)   | 0.163           |



**Figure 1.** Nasal nitric oxide values (nNO) in patients with and without nasal polyps. \* =  $p < 0.001$ .



**Figure 2.** Correlation between ACQ and nasal nitric oxide (nNO) ( $R^2 = 0.253$ ,  $p = 0.002$ ).

**Table 3.** Determinants of asthma control according to ACQ (dependent variable).

| PARAMETER          | Mean square | <i>F</i> | <i>p</i> -value |
|--------------------|-------------|----------|-----------------|
| Corrected model    | 1.207       | 1.656    | 0.144           |
| Intercept          | 1.735       | 2.380    | 0.133           |
| Gender             | 1.283       | 1.760    | 0.195           |
| Age                | 0.407       | 0.559    | 0.461           |
| Atopy              | 0.368       | 0.506    | 0.483           |
| BMI                | 0.483       | 0.662    | 0.422           |
| BUD equivalents    | 0.003       | 0.004    | 0.948           |
| FE <sub>NO</sub>   | 0.000       | 0.000    | 0.989           |
| Jaw <sub>NO</sub>  | 2.513       | 3.448    | 0.073           |
| Calv <sub>NO</sub> | 0.256       | 0.351    | 0.558           |
| nNO                | 5.856       | 8.035    | <b>0.008</b>    |

BUD = Budesonide.

Significant *p*-values have been marked in **bold font**.



Patients with CRSwNP had significantly lower values of nNO ( $311.0 \pm 221.0$  ppb) compared to the other patients ( $853.9 \pm 365.2$  ppb) and to controls ( $887.5 \pm 252.0$ ) ( $p < 0.001$ ) (figure 1). A significant correlation was found between nNO and ACQ ( $R^2 = 0.253$ ,  $p = 0.002$ ) in patients with CRS (figure 2).

No difference in mean values of FE<sub>NO</sub> was detectable between patients with CRSwNP versus CRSsNP and/or versus patients without CRS.

Multiple regression analysis (table 3) with age, gender, atopy, BMI, equivalents of inhaled budesonide, FE<sub>NO</sub>, Jaw<sub>NO</sub>, Calv<sub>NO</sub> and nNO as independent variables showed that nNO was the only significant determinant of poor asthma control ( $p = 0.008$ ).

Smoking status and non-steroidal anti-inflammatory drugs (NSAIDs) intolerance were not included into the analysis as only a minority of patients reported these characteristics (only one smoker patient with controlled asthma, and four NSAIDs intolerant patients equally distributed between controlled and uncontrolled asthma groups).

## Discussion

The main result of our study is that low nNO values, which are significantly associated to CRSwNP, are also significantly correlated to asthma control as assessed by ACQ. The best explanation for the inverse relation between nNO and asthma control may be the high prevalence of CRS in our population of asthmatics (41.5%). It is known that CRS is a comorbidity which may negatively influence the severity and control of asthma [6, 17, 18]. Nasal NO levels have been reported to be greatly influenced by the degree of sinus involvement, with an inverse correlation between nNO levels and the extent of sinus disease as documented by CT scan, endoscopic score and polyp grades [11, 19]. So it is not surprising that the inverse relationship between nNO and asthma control was even more significant in our patients with CRS, suggesting that severe CRS has a major impact on asthma control.

On the other hand, we did not find any significant correlation between FENO and asthma control. The lack of correlation between FENO and asthma control has been previously reported both in adults and children [20–22]. A weak correlation between asthma control, evaluated with ACT, and FENO was described by Japanese authors in a cohort of 105 patients with a high prevalence of uncontrolled asthma (60%) [23]. A better correlation between FENO and childhood ACT ( $r = -0.51$ ;  $p < 0.001$ ) was found by Piacentini *et al* [24] in 47 children with a new diagnosis of asthma and not on regular treatment. The same authors failed to find the same significant relationship in 153 children on current asthma treatment. All our patients were on treatment with inhaled steroids, which are known to decrease FENO values in a dose-dependent manner [25].

The results of our study show that assessment of asthma control, based primarily on symptoms evaluation through standardized questionnaires, does not reflect airway inflammation as assessed by exhaled NO. Some patients had poor asthma control based on ACQ score with normal nitric oxide levels. Probably in these subjects symptoms could depend on other conditions such as hyperventilation, upper airway disease related to rhinitis and CRS, or neutrophilic airway inflammation. Other patients appeared to be controlled according to ACQ, despite increased FENO values suggestive of eosinophilic airway inflammation. It is well known that persistent airway inflammation may be observed also in patients with asymptomatic asthma [26] possibly leading to airway remodeling and fixed bronchial obstruction [27]. It is interesting that most of these patients have CRSwNP, comorbidity which has been related to eosinophilic airway inflammation [28].

In the present study CRSwNP was the only asthma comorbidity associated to low nNO values. We suggest that combined measurement of FENO and nNO, which are both easy to obtain in clinical practice, may help clinicians to find the patient who may gain advantage to achieve better asthma control from a combined treatment of upper and lower airway inflammation [23]. Nasal NO is a valuable objective measurement in monitoring medical and surgical therapy for CRS, and increase in nNO has been related to successful treatment of CRS [18].

While increase in nNO has been shown to correlate with patients' own perception of improvement of sinusitis, no data are available about the correlation between the changes in nNO and the changes in asthma control in patients with asthma and CRS.

A possible limit of this study is that it is a cross-sectional study but we think that it is strengthened by the fact that it is a real-life observational study, therefore not influenced by any selection bias.

In conclusion, our results confirm that nNO is decreased in CRSwNP and show, for the first time, that it is negatively related to asthma control, underlying the role of nasal polyposis as an influent comorbidity on asthma control. It is conceivable that this biomarker reflects aspects of airway inflammation which are related both to symptoms and airway function of asthma, as asthma control was assessed by ACQ, which combines symptoms and FEV<sub>1</sub> scores.

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